REMARKS

Claims 1-16, 18 and 19 are pending. Claims 1-12, 14-16, and 18 are withdrawn from consideration in the present application. Claims 13 and 19 are rejected. Applicant appreciates that all of the previously stated rejections have been withdrawn in light of the amendments to the claims and specification. Claim 19 is amended to specify that a fragment of the second antibody is a "binding" fragment. No issue of new matter arises by way of this change as support may be found in the specification at page 14, line 3 of the published PCT/GB02/02779, from which the instant application is a continuation.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claim 19 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. The Examiner says that the specification enables only compositions comprising antibodies or antigen binding fragments, but allegedly does not enable any antibody fragments. The Examiner offers that Applicant may obviate the rejection by amending the claim to include language directed to an antigen binding fragment of the second antibody. Claim 19 is amended to specify that a fragment of the second antibody is a "binding" fragment thereby obviating the rejection.

Rejection under 35 U.S.C. § 103

The Examiner rejects claims 13 and 19 under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,812,339 (effective date October 20, 2000) in view of U.S. Patent Application Publication No. 2005/0159373 (effective filing date March 22, 2001) and Marin *et al.* (*Br. J. Cancer* 76: 923-9, 1997). U.S. Patent 6,812,339 allegedly teaches amino acid sequence 10387 which is 99.9% homologous to SEQ ID NO: 1 of the instant application, a DTD polypeptide. Moreover, antibodies directed against amino acid sequence 10387 are allegedly identified as modulators (citing, Column 34, lines 36-41; Column 36, line 59-column 37, line 2) that can be administered to treat disease (*citing*, Column 35, Columns 58-65). The Examiner acknowledges that the patent does not teach that the human disease is breast cancer and that the antibodies are immunoconjugates.

The Examiner says that U.S. Publication No. 2005/0159373 teaches an antibody as well as fragments and immunoconjugates against the same target sequence for the treatment of breast cancer. Further, Marin *et al.* allegedly teach the DTD enzyme is associated with breast tumors (citing, page 1, section 0011; page 19, sections 0198-0204 and 0209-0212; and page 20, sections 0221 and 0222). The Examiner therefore says that it would have been *prima facie* obvious to implement the teachings of U.S. Patent 6,812,239 to treat breast cancer in the method of administering modulators to treat human disease. It was also allegedly *prima facie* obvious to treat breast cancer, given that DTD is recognized as a breast cancer marker. Motivation to combine the teachings of the references is allegedly based on the sequence homology (99.9%) between the target amino acid sequence and sequence 10387 and U.S. Patent No 6,812,339 and 2005/0159373, which both allegedly teach treating subjects with essentially the same antibodies.

Regarding U.S. Patent 6,812,339

Applicant respectfully traverses. U.S. Patent 6,812,339 does not teach or suggest a method to treat cancer. Moreover, the patent does not even teach or suggest a specific antibody of the present application.

U.S. Patent 6,812,339 teaches certain single nucleotide polymorphisms and hypothesizes that one or more of these may cause or be associated with certain disease states. The patent teaches a large number of different sequences. The sequence identification numbers extend as high as 23,778. These sequences have no particular link or relationship to each other. Furthermore, U.S. Patent 6,812,339 does not teach or suggest any relation of any sequence to any specific disease but rather only makes general comments that the sequences may be useful in the treatment of diseases. Applicant submits that the corresponding application as filed was clearly speculative at the time it was filed.

The Examiner says that U.S. Patent 6,812,339 provides a specific teaching regarding DTD, and that U.S. Patent 6,812,339 would be a starting point for one of ordinary skill in the art, working in the relevant field because the sequence is disclosed. Applicant respectfully disagrees because i) DTD is not mentioned in the patent; ii) there is no discussion of any specific biological function of the relevant sequence in the patent; and iii) the specific nucleotide sequence referred to by the Examiner needed to have been selected from a large number of

sequences having different functions. As such, Applicant submits that U.S. Patent 6,812,339 is not a realistic starting point for the skilled person because this document does not teach or suggest that the particular sequence identified, 10387, is of more interest than the plethora of other sequences contained therein. Therefore, selecting this sequence from this document is based on knowledge of the benefits of the target according to the presently claimed invention. In fact Applicant submits that the only utility supported by the disclosure of the U.S. Patent 6,812,339 is use of the sequences therein as probes and general diagnostic tools.

Applicant further submits that the modulator and antibody language referred to by the Examiner are simply template (boiler plate) language referring to thousands of sequences. As such, Applicant respectfully submits that the Examiner is using hindsight and with knowledge of the present invention in constructing the rejection. The courts have long ruled that such a hindsight reconstruction of a claimed invention is not permitted. Such a hindsight reconstruction does not constitute a proper *prima facie* case of obviousness.

Regarding Marin *et al.*

The Examiner says that Marin *et al.* teach that the DTD enzyme is associated with breast tumors. Applicant submits that Marin *et al.* teach the theory that certain enzymes in tumor tissue may be capable of selectively reducing or metabolizing certain prodrugs *in vivo* to generate a compound more toxic than the parent compound. Therefore, the level of the relevant enzyme in tissue may be important. Marin *et al.* investigate the role of DTD as a potential activator of cancer chemotherapy drugs. Part of this investigation involved determining the levels of expression of DTD in cancer tissue samples. This analysis showed that DTD was over expressed in some samples, such as certain breast cancer samples. Marin *et al.* concluded that "DTD-mediated chemotherapy should be indicated only for individual patients with a demonstrated very high level of activity of this particular enzyme measured in tumor biopsy specimens". Thus Marin *et al.* envision giving a normal chemotherapeutic agent for activation to individuals identified as having high levels of DTD expression in tissue samples taken from their cancer. This is a completely different mechanism to that employed in the currently claimed invention. Therefore, Marin *et al.* do not teach or suggest using DTD as a target for cancer therapy (particularly breast cancer therapy). Likewise, Marin *et al.* do not teach or suggest employing antibodies specific to DTD in therapy.

Regarding U.S. Publication No. 2005/0159373

The Examiner says that U.S. Publication No. 2005/0159373 teaches "implementing an antibody, as well as fragments and immunoconjugates against the same target for the treatment of breast cancer." Applicant submits that U.S. Publication No. 2005/0159373 teaches a protein named WUP. Applicant respectfully adds that none of the sequences disclosed in U.S. Publication No. 2005/0159373 are similar to DTD. Applicant submits his willingness to submit scientific evidence in the form of sequence alignment and blast search results to demonstrate this lack of similarity to DTD. As such, U.S. Publication No. 2005/0159373 does not teach or suggest "implementing an antibody, as well as fragments and immunoconjugates against the same target for the treatment of breast cancer."

The Examiner has failed to establish a *prima facie* case of obviousness based upon the primary and secondary references

Applicant submits that one of ordinary skill in the art would not find a motivation to combine U.S. Patent 6,812,339 and Marin *et al.* because U.S. Patent 6,812,339 does not teach or suggest anything specific about DTD. Rather, U.S. Patent 6,812,339 merely provides the nucleotide sequence encoding the same. There is no teaching or suggestion that DTD may be implicated in breast cancers nor any reasonable expectation that such would be the case. Secondly, even if, *assuming arguendo*, the teachings of these two references are combined, the combination does not provide the presently claimed invention. Rather, combining the references merely provides modulation of DTD to increase the levels of the enzyme in cancerous tissue so that it would be a more effective activator of a chemotherapeutic agent (i.e. to render the latter more toxic in the tissue than the parent compound). The present invention provides a method of treating breast cancer by modulating the activity of DTD with an antibody specific therefor. Thus, the Examiner has failed to set forth a proper *prima facie* case of obviousness based upon these two references.

U.S. Publication No. 2005/0159373, as noted, *supra*, fails to cure any of the deficiencies of U.S. Patent 6,812,339 or Marin *et al.* thereby still failing to teach or suggest the elements of the claimed invention. Still further, since U.S. Publication No. 2005/0159373 teaches an unrelated protein named WUP, Applicant submits that there is no motivation to combine its

teachings with those of U.S. Patent 6,812,339 or Marin *et al.* For these additional reasons, the Examiner has also failed to set forth a proper *prima facie* case of obviousness based upon all three of the references combined or any combination of two of the three references.

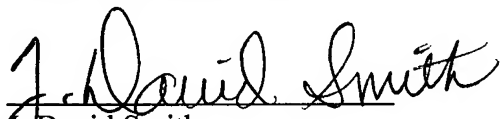
Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is believed that the claims are in condition for allowance. In the event that there are any issues that may be resolved by telephone, the Examiner is respectfully urged to call the undersigned at the telephone number indicated below.

Respectfully submitted,



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